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PATENT COOPERATION TREATY

PCT

REC'D 18 JUN 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

3

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NEB-164-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/13292	International filing date *(day/month/year)* 12 MAY 2000	Priority date *(day/month/year)* 14 MAY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/70; C12N 15/00 and US Cl.: 435/5, 7.1, 7.4, 69.1, 69.2, 70.1, 963; 530/350		
Applicant NEW ENGLAND BIOLABS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 DECEMBER 2000	30 MAY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENNETT CELSA Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/13292

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-36, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 37-41, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages 1-12, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages 1-10, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	10-20	YES
	Claims	1-9	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-20	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-9 lack novelty under PCT Article 33(2) as being anticipated by Larsen et al. (US Pat. No. 5,272,07, 12/93).

Larsen et al. teach the use of expression vectors (e.g. lambda phage) for recombinantly incorporating selenocysteine (SeCys) into a peptide as part of a vector surface protein fusion protein (see e.g. col 5, line 63 to col. 6, line 60; col. 7 line 35-45; col. 9 line 35-60; col. 15, line 60 to col. 16 line 8; col. 20, line 40-57; examples; col. 33 line 18-43; col. 35, line 13-line 25; patent claims 3-15.

Claims 1-9 lack novelty under PCT Article 33(2) as being anticipated by Leonard et al. (US Pat. No. 5,700,660, 12/97).

Leonard et al. teach the use of conventionally known recombinant expression vectors (e.g. baculovirus vectors: e.g. see col. 19, lines 5-15) to "transduce" "transform" or "transfect" procaryotic/eucaryotic cells for recombinant incorporation of selenocystein into a peptide e.g. as part of a surface protein fusion protein (e.g. see col. 3, line 24-35; col. 5, lines 25-35; col. 13, lines 42- col. 14, line 58; col. 18-19; patent claims 1-16), with further "nucleophilic substitution" (e.g. see col. 19, lines 24-35) of SeCys being possible for purposes of screening.

Claims 10-20 lack an inventive step under PCT Article 33(3) as being obvious over Dower et al. (US Pat. No. 5,432,018, 7/95) in view of Pegoraro et al. (J. Mol. Biol). Larsen et al. and/or Leonard et al.

Dower et al. disclose the use of phage peptide libraries for screening ligands by binding to receptor (e.g. See Abstract; col. 4; Examples, especially example III; and patent claims).

Dower et al. also teach diversification of phage-produced peptide libraries (col. 6-14) including amino acid modification of the 20 naturally occurring amino acids by "chemical modifications" including carboxy terminal amidation, introduction of enzyme substrate peptide structure, metal (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
coordination complexes (E.g. to cys) and the introduction of conformational constraints using cysteine incorporation and formation (e.g. by oxidation) of disulfide bonds (e.g. see col. 9-12).

The Dower et al. reference fails to teach the use of SeCys in its phage peptide libraries for screening.

However, the Pegoraro et al. reference teaches that substitution of Secys for cys when introducing conformation constraints is desirable due to the "high stability of the deselenide group toward reducing agents (e.g. see abstract).

Thus the Pegoraro et al. reference provides motivation to substitute SeCys for Cys during the "chemical modification" of the Dower et al. libraries to realize the increased stability of SeCys.

Further, one of ordinary skill in the art would further be motivated to incorporate SeCys into the Dower phage display library at the onset in order to increase diversity (e.g. synthesize more potential ligands) by use of 21 instead of the 20 naturally occurring amino acids.

In this regard, the use of conventionally known recombinant expression vectors (e.g. baculovirus vectors) to "transduce" "transform" or "transfect" procaryotic/eucaryotic cells for recombinant incorporation of selenocystein into a peptide with further "nucleophilic substitution" of SeCys for purposes of screening is known in the art. See e.g. Larsen and Leonard references described above.

Thus, modification of the Dower et al. phage peptide library technique to utilize SeCys would have been obvious to one of ordinary skill in the art in order to increase peptide bond stability and increase peptide diversity.

Claims 1-20 meet the criteria set out in PCT Article 33(4).

---------- NEW CITATIONS ----------
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/13292

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/70; C12N 15/00
US CL :435/5, 7.1, 7.4, 69.1, 69.2, 70.1, 963; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 7.1, 7.4, 69.1, 69.2, 70.1, 963; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: DERWENT, USPATENTS, EPO ABSTRACT; STN: CAPLUS, MEDLINE, EMBASE, BIOSIS, WPIDS.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,272,078 A (LARSEN et al.) 21 December 1993, see entire patent.	1-9 --- 10-20
X --- Y	US 5,700,660 A (LEONARD et al.) 23 December 1997, see entire patent.	1-9 --- 10-20
Y	PEGORARO et al. Isomorphous Replacement of Cystine with Selenocystine in Endothelin: Oxidative Refolding, Biological and Conformational Properties of [Sec^3,Sec^{11},Nle^7]-Endothelin-1. J. Mol. Biol. 04 December 1998, Vol. 284, No. 3, pages 779-792, especially abstract.	10-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 AUGUST 2000	Date of mailing of the international search report 07 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENNETT CELSA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/13292

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,432,018 A (DOWER et al.) 11 July 1995, see entire patent, especially col. 6-15, Examples III and IV.	10-20
A,P	Database CAPLUS on STN. Abstract No. 132:147279. CHO et al., "Construction of a hexapeptide library using phage display for bio-panning". J. Microbiol. June 1999, Vol. 37(2), pages 97-101.	10-20
A	WO 98/39660 A1 (EVOTEC BIOSYSTEMS GMBH) 11 September 1998, see Abstract.	1-20